

# Time dysperception perspective for acquired brain injury

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Distortions of time perception are presented by a number of neuropsychiatric illnesses. Here we survey timing abilities in clinical populations with focal lesions in key brain structures recently implicated in human studies of timing. We also review timing performance in amnesic and traumatic brain injured patients in order to identify the nature of specific timing disorders in different brain damaged populations. We purposely analyzed the complex relationship between both cognitive and contextual factors involved in time estimation, as to characterize the correlation between timed and other cognitive behaviors in each group. We assume that interval timing is a solid construct to study cognitive dysfunctions following brain injury, as timing performance is a sensitive metric of information processing, while temporal cognition has the potential of influencing a wide range of cognitive processes. Moreover, temporal performance is a sensitive assay of damage to the underlying neural substrate after a brain insult. Further research in neurological and psychiatric patients will clarify whether time distortions are a manifestation of, or a mechanism for, cognitive and behavioral symptoms of neuropsychiatric disorders.

**Keywords:** interval timing, cognitive dysfunction, time distortions, brain damage, information processing

*"Time is what prevents everything from happening at once."*

*John Wheeler, physicist*

## INTRODUCTION

As both perception and action take place over time and evolve over time, timing is a fundamental component of information processing in the central nervous system. Indeed, our ability to time events in the seconds to minutes range [*interval timing*, Ref. (1, 2)] determines not only the subjective experience of time-in-passing, but also structures our action and cognition allowing us to determine what is happening in our environment and when to respond to events.

Since the representation of time is necessary to appreciate environmental contingencies and estimate predictive relations between events, and between events and responses, timing helps us to interpret reality. Moreover, temporal cognition is a fundamental "*basic unit of ability*" on which other cognitive and behavioral processes are based (3) as for example, complex cognitive functioning is largely dependent on underlying temporal constraints (4). In this sense, temporal processing has the potential of influencing a wide range of cognitive processes [e.g., Ref. (5)].

On the other hand, since interval timing is defined as the ability to perceive, remember, and organize behavior around periods in the range of seconds to minutes, the cognitive apparatus required by this ability include several neuropsychological functions. Supporting cognitive processes comprise allocation of attentional resources to the perception and encoding of incoming temporal information, storage and retrieval of the temporal percept in a long-term memory, and comparison with other percepts in working memory.

Given the inextricable functional interrelation between interval timing and supportive neuropsychological processes, the neuroscientific study of timing can be a model system to study cognitive dysfunction (6). In fact pathophysiological distortions in time might depend on and reflect neuropsychological deficits characteristic of definite neuropsychiatric disorders. Specifically, disrupted timing has been reported in illnesses associated primarily with dopaminergic and fronto-striatal dysfunctions (7, 8) [e.g., Parkinson's disease (PD), schizophrenia (SZ), Huntington's disease (HD), attention-deficit hyperactivity disorder (ADHD), see **Table 1**] (3, 9, 10).

However, since both the dopaminergic system and fronto-striatal circuitry support other cognitive processes such as working memory [e.g., Ref. (11)] and reward based-learning [e.g., Ref. (12), Ref. (13)], either required for accurate timing, questions still remain concerning whether increased timing variability in some neuropsychiatric disorders arises from non-temporal sources or originates from defective interval timing mechanisms. Similarly, multiple lines of evidence (fMRI, lesion, and TMS studies) suggest that prefrontal, frontal, and parietal cortices (14–18), predominantly in the right hemisphere, are crucial for time estimation in the second-to-minute range, although it is not clear whether these brain areas are directly related to time perception, or if they sub serve the non-temporal processes (working memory, recall, and attention) necessary for cognitively controlled time measurements. Indeed, it has been argued (19) that the observed activity in prefrontal and parietal cortices during cognitive controlled temporal tasks could simply reflect the increased sustained attention or working memory demands required by timing longer durations.

Following this line of argument, interval timing can serve a crucial role in models of cognitive dysfunction following brain injury.

**Table 1 | Representative studies reporting pathophysiological distortions in time perception and timed performance in neuropsychiatric populations.**

Neuropsychiatric condition	Timing paradigm	Individual differences	Reference
Parkinson's disease (medicated)	Explicit motor (60) (finger tapping) and non-motor tasks (109) (interval discrimination; duration bisection) in the second and sub-second range	PD groups impaired both in motor timing and time perception in the sub-second and seconds time range	Harrington et al. (60); Smith et al. (109)
Patients with Parkinson's disease (both on and off medication)	Temporal generalization, bisection, threshold determination, verbal estimation, and a memory for duration task	Stimulus timing performance in patients with PD is relatively normal; small differences may be found on tasks where two stimuli are presented on each trial, possibly as a result of attentional or executive problems	Wearden et al. (110)
	Externally and internally paced finger tapping (111); interval discrimination in the seconds range (112) during functional imaging	Impaired motor timing is consequent to insufficient striatal activity and corticostriatal connectivity (111); the source of impaired time perception in PD is not exclusively temporal, as functional dysfunctions in areas associated with working memory and executive processes were also observed (112)	Jahanshahi et al. (111); Harrington et al. (112)
Patients with pre-symptomatic and symptomatic Huntington's disease	Explicit motor timing (113) (time estimation) and perceptual time discrimination (113, 114) during fMRI	Even premanifest HD subjects have disrupted time estimation performance which correlates with differences in striatal function; performance declines if timing is embedded in motor processes (113)	Beste et al. (113); Paulsen et al. (114)
Patients affected by schizophrenia	Verbal estimation (115), interval discrimination (116); motor timing [repetitive tapping (116, 117) and time production (118)]	Patients overestimate interval duration when verbally reporting it (115) or during repetitive tapping (117) and underestimate interval duration during time production tasks (118); attentional disturbances (119), working memory deficits (120) or a dysfunction at the decision stage (116) may explain the observed time perception impairment	Tysk (115); Carroll et al. (117); Wahl and Sieg (118); Penney et al. (119); Roy et al. (120); Papageorgiou et al. (116)
Patients with attention deficit hyperactivity disorder	Finger tapping (121–123); interval discrimination (124); interval reproduction (125); interval production (126)	A highly consistent pattern of motor timing abnormalities has been reported both in the sub-second and supra-second intervals scale and in different age groups (121–123). Investigations of duration discrimination, reproduction, and production provide reliable evidence for impairments in ADHD (124–126)	Zelaznick et al. (121); Topla and Tannock (122); Gilden and Marusich (123); Smith et al. (124); Huang et al. (125); Marx et al. (126)

Actually, since different patterns of brain activity can be elicited by time measurement, and that this is partially dependent upon the nature of the task as well as the participant's neurological status (20), interval timing could be a valuable construct in neuropathology (6). Specifically, timing performance might be a sensitive metric of cognitive functioning and a reliable assay of damage to the underlying neural substrate (21) [see for example, the hypothesis of a white matter connectivity damage in mild traumatic brain injury (TBI) deriving from the observation of impaired predictive timing during smooth pursuit eye movements (21)].

Assuming that diverse disorders have their own signature regarding measures of timed behavior, in the present paper we posit that interval timing can be a valid heuristic to explain, in brain damaged populations: (i) the nature of specific cognitive deficits, (ii) the relationships between time estimation and cognition as time judgments are investigated in patients who present memory and attention dysfunctions, and (iii) the essence of such relationship, i.e., whether the correlation between timed

and other cognitive behaviors results from specific co-variation of common temporal processes or from coincidental co-variation in the cognitive components (e.g., working memory) shared by the two functions. Indeed, it has been suggested that temporal processing may reflect a “cognitive primitive,” a fundamental neuropsychological process that has a broad influence on cognitive function, constituting part of the functional architecture for cognition (22, 23).

### ISOLATING CHANGES IN DIFFERENT INFORMATION PROCESSING STAGES

The most influential model in the psychological timing literature, the *Scalar Expectancy Theory* (SET) or *internal clock model* (24–26) assumes that at the onset of a to-be-timed event, a switch controlled by attention closes and allows pulses emitted by an internal pacemaker to be collected into an accumulator; the current pulse tally held in working memory is then compared with a previously stored value in reference memory; when the two

values match closely enough, a decision rule operates to produce an estimate of time. According to this account, interval timing is highly dependent on other cognitive resources as arousal, vigilance and attention (27–29), working memory, episodic memory, and decision-making (9, 30, 31), such that it may be derivative of these other processes (32, 33). Although the model remains contentious and has a number of competitors, it can easily accommodate individual and pathophysiological differences in timing by adjusting the function of any one of its components. Specifically, considering the plethora of tasks thus far used to experimentally test timing abilities, one can dissect, from the behavioral data gathered in different timing paradigms, the differential contribution of intervening cognitive processes to timing performance. For example, the ability to time short intervals (milliseconds) may be more related to an internal timing mechanism, while longer intervals (seconds) are more related to episodic and working memory (34). Moreover, targeted manipulations can be designed to differentially affect the relative function of the information processing steps described by the SET (35), as the clock stage is influenced by dopaminergic manipulations, and the memory stage by cholinergic manipulations (36, 37).

However, in spite of the fact that contextual factors (i.e., the timing task used) impact temporal performance and the relative contribution of intervening cognitive processes, timing, and time perception in humans (as well as in animals) have striking regularities, as revealed by psychophysical methods used to quantify sensory responses to physical stimuli. Specifically, not only is the intensity of the internal perception linearly related to the magnitude of external stimulation (subjective time increases with physical time), but also increases in the magnitude of a physical stimulus produce proportional increases in the variance of the perception (i.e., it is more difficult to time precisely for longer durations). Deviations from such properties in specific populations are most informative and allow us to make reasonable conjectures as to what mechanisms might be involved in performance differences since for example, damage to and/or pharmacological blockade of corticostriatal circuits impairs the regulation of clock speed as a function of the target duration such that longer intervals will be timed more precisely than shorter intervals, owing to the loss of the scalar source of variability in clock speed (37).

Pertaining to the functional taxonomy of timing, a crucial distinction is made between processes engaged in tasks for which the goal is to provide an overt estimate of elapsed time (explicit timing) as opposed to tasks in which the goal is non-temporal but can, nevertheless, be facilitated by an apparently incidental temporal context [implicit timing, Ref. (38, 39)]. Timing functions are further subcategorized into motor timing (i.e., adjustment of behavior or motor responses to externally or internally defined timeframes, measured in the range of milliseconds and seconds) and perceptual timing (i.e., time estimation and discrimination, also measured in intervals of milliseconds and seconds) (38). Some of these tasks have been originally developed for studying timing in animals [e.g., Ref. (24)] and later extensively applied to humans to test the ways in which different groups (e.g., children, student-age adults, and the elderly) differs [e.g., Ref. (29)].

Actually, most timing paradigms co-measure other non-temporal processes (such as sustained attention or the ability

to temporarily hold and manipulate interval representations) depending on the temporal domain they cover. For example, time reproduction relies on working memory functions and the ability to delay a response. Thus, several investigations have tried to examine the relationship between temporal and non-temporal processes. Specifically, time perception varies as a function of selectivity, since attentional resources are limited in time and temporal performance is compromised when attention is overloaded [see Ref. (40) for a meta-analysis on the effect of cognitive load on duration judgments]. It follows that performance in timing tasks is necessarily confounded with attention to time. However, paradigms have been developed to isolate neural networks supporting attention to temporal information from those supporting timing functions *per se* (41) or involved in directing attention to non-temporal stimulus features (42, 43). Temporal attentional orienting can be also modulated pharmacologically, as clonidine, an  $\alpha 2$  adrenoceptor agonist which impairs noradrenergic functioning, selectively affects the ability to direct attentional resources to a particular time-point (44), but not time estimation (45). Such observation might be specifically relevant to disorders as ADHD or frontal type dementia in which modulation of noradrenergic release appears to remediate specific attentional functions by attenuating the influence of task-irrelevant information (46).

Also the effective speed of the internal clock can be behaviorally and pharmacologically manipulated, thus affecting judgments of duration: since they directly depend on the number of pulses accumulated, the more pulses that are accumulated, the longer the duration is judged to be, and vice-versa. On the one hand, the rate of subjective time can be changed by producing even slight increases in arousal (e.g., by presenting trains of clicks or a visual flicker) (27). Conversely, as interval timing has been hypothesized to rely on an optimal level of dopaminergic activity in corticostriatal circuits (37), systemic injections of drugs that are believed to promote dopaminergic function (e.g., methamphetamine, cocaine, and nicotine) will determine the underestimation of interval duration (37, 47). This pattern of behavioral change, termed the “clock pattern” (37), is due to the fact that the standard duration representation (e.g., 400 ms) is generated by a normal clock speed while the comparison representations are generated by a putatively faster clock, so that the criterion number of clicks is accumulated in a shorter period (e.g., 350 ms). In a complementary fashion, drugs that are believed to inhibit dopaminergic function (e.g., antipsychotics) produce the overestimation of interval duration due to a decrease in clock speed in the testing phase, so that the criterion amount of clock ticks is accumulated more slowly (37, 48).

Changes in temporal memory and decision processes may also affect event timing and few studies have tried to manipulate the memory stage (49, 50) essentially by increasing temporal memory load (which results in increased variability – i.e., decreased accuracy – in duration judgments). Similarly, a secondary memory task markedly impairs temporal processing of intervals in the range of seconds, since the latter is particularly mediated by memory processes (51). Furthermore, the representation of durations in memory is closely related to decision processes, and a veridical feedback improves the representation of durations in reference memory and modifies the decision criteria.

Pharmacological-induced changes in temporal memory are typically produced by cholinergic drugs. Indeed, anticholinesterases such as physostigmine, produce proportional underestimations, and acetylcholine receptor antagonists such as atropine, produce proportional overestimations (37, 47). The hallmark of the specific drug effect on temporal memory is the gradual but long-lasting change in temporal judgments which fails to re-normalize with continued training under the drug (52).

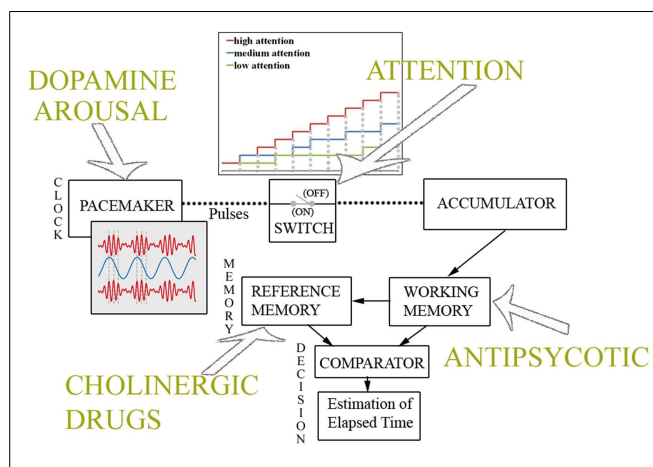
Lastly, since interval timing and working memory are intricately linked in a variety of situations, any behavioral or pharmacological treatment that interferes with maintaining the activation of memory units or attentional processes in working memory may hamper the temporal processing of longer intervals (53). In several pharmacological studies (53, 54), it has been shown that both dopamine antagonists and benzodiazepines that directly affect information processing in working memory, also induce impaired temporal processing of intervals ranging from 1 to 1.4 ms. **Figure 1** depicts the cognitive model of time perception as specified by the SET. Pharmacological and cognitive factors affecting different stages of the temporal information processing are also sketched.

## TIME PERCEPTION IN BRAIN DAMAGED POPULATIONS

### LESION STUDIES: IDENTIFYING CRITICAL BRAIN REGIONS

Experimental findings heavily implicate the cerebral cortex, along with the basal ganglia (BG) and cerebellum, in the cognitive processes involved in event timing. In particular, patients with frontal lesions exhibit greater variability [i.e., poorer discrimination, Ref. (55)] when the processing of supra-seconds intervals is required (56, 57). The right prefrontal cortex seems to be involved in longer intervals estimation (14, 16, 58), probably because of its role in other non-temporal processes (sustained attention and working memory) necessary for cognitively controlled time measurements. Timing of longer intervals is also impaired after a lesion, as well as after repetitive transcranial magnetic stimulation (rTMS) functional inhibition (59) to the right parietal lobe (58), thus suggesting that a right prefrontal inferior parietal network is probably engaged in duration estimation (60) especially for longer durations (61). Lesions to the right lateral frontal lobe also prevent the decrease in reaction time that is usually seen in normal subjects when stimulus onset can be anticipated on the basis of the increasing probability of target onset over time (hazard function) (62) or via temporal pre-cues (63). Also patients with right but not left medial temporal lobe resection are impaired in the discrimination of auditory durations in the millisecond range (64), of visual supra-seconds intervals (65) and in the retention of auditory but not visual rhythms (66).

Studies involving subjects with focal lesions to the BG are less conclusive. Indeed, unilateral damage to the BG does not determine timing impairments, at least in motor timing (67), nor abnormalities in temporal orienting tasks in which subjects make deliberate use of temporal pre-cues to anticipate when a target will appear (63). However, even if patients with bilateral lesions to the BG perform relatively well in time estimation tasks, they perform poorly when they are required to maintain rhythmic tapping (68), thus suggesting that BG are essential in reproducing a motor representation of a timed inter-trial-interval (ITI). A bilateral BG dysfunction with significant, disabling clinical signs (68)



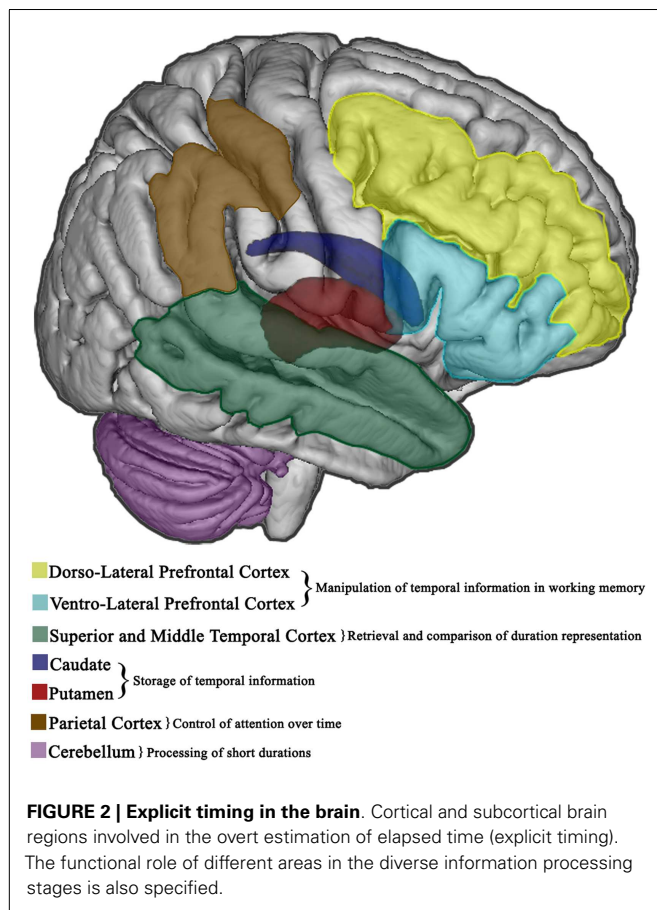
**FIGURE 1 | Cognitive model of time perception.** Information processing model of interval timing as specified by the Scalar Expectancy Theory. As depicted in top panel, the pacemaker speed is affected by dopamine levels and arousal, while attention to time modulates the switch. When attention is high, the estimate of elapsed time grows according to the clock rate, while if attentional resources are overloaded (medium, low attention to time), the switch fluctuates between a closed and an open state, resulting in the underestimation of physical duration. As shown in bottom panel, cholinergic drugs induce changes in temporal memories, whereas antipsychotic medications affect the working memory processes involved in the estimation of elapsed time.

seems specifically to determine deficits in sub-second timing tasks with a heavy motor component, congruently with accounts that emphasize the role of BG in action.

Also patients with cerebellar damage show marginal (69), non-selective (70) perceptual timing deficits restricted to the sub-second range (55), thus suggesting that the role of cerebellum might be limited to the temporal processing of short durations. Moreover, the cerebellar circuit seems to be vital to performing accurate, rapid rhythmic timing at the fastest intervals (71), as cerebellar patients show increased variability during the synchronization phase at the shortest inter-stimulus-interval (ISI), while patients with neurodegenerative disorders affecting the BG demonstrate less variability but altered accuracy (71, 72). Additionally, cerebellar timing deficits extend to tasks in which patients are required to use the constant spatio-temporal stimulus dynamics to predict its spatio-temporal trajectory (*spatio-temporal prediction*) (73) and show impairments in predictive motor timing, along with difficulties integrating visual stimuli with motor output (74).

Taken together such findings indicate that the right prefrontal cortex and BG are essential in explicit duration estimation, while temporal predictions are established in left premotor-cerebellar-parietal circuits (37, 75), and potentially updated on-line in the right prefrontal cortex (76). However, the abovementioned regions have functionally dissociable roles as the right frontal cortex may serve to manipulate temporal information in working memory, while the value is stored in other subcortical regions (i.e., caudate and putamen) (69, 77); subsequent retrieval and comparison of duration representations entail the right temporal cortex (77) which is probably involved in the decision stage (64, 78). Further,

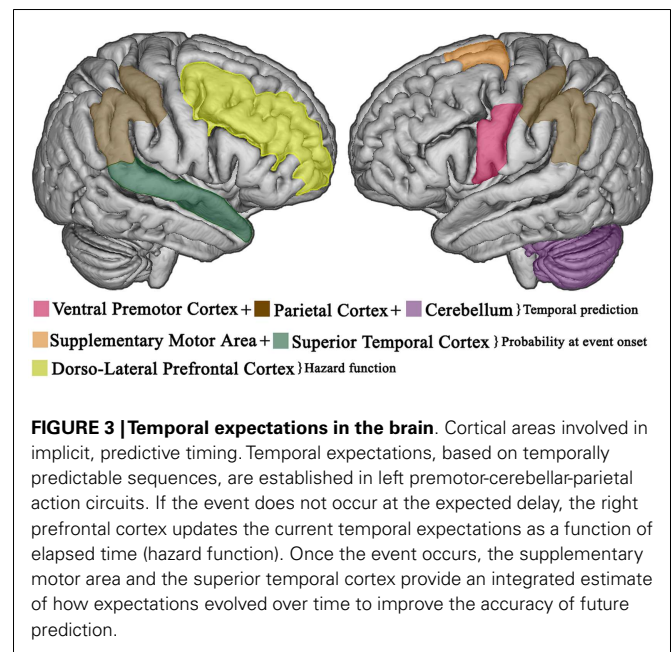




the right parietal lobe may have a crucial role in tasks that require the control of attention over time (79). **Figures 2 and 3** show the brain regions involved in the explicit and implicit estimation of time intervals as well as their functional role in the processing of temporal information.

#### TIME PERCEPTION IN AMNESIC PATIENTS: THE ROLE OF MEMORY PROCESSES

Neuropsychological studies in amnesic patients, or those with Korsakoff's syndrome (80–82) set the opportunity to evaluate the theoretical model of interval timing from the point of view of organic memory disorder. Indeed, since Meck's first report (78) numerous studies have demonstrated reliable changes in the accuracy and precision of interval timing following a variety of techniques impacting hippocampal function (e.g., transection of the fimbria fornix, lesions of the medial septal area, resection of the temporal lobe, selective lesions of the dorsal hippocampus, and destruction of the entire hippocampus [see Ref. (6) for a review]). Rats and mice with lesions of the hippocampus and related areas, when faced with tasks requiring them to estimate or reproduce a specific duration, respond earlier on average than normal subjects indicating an over estimation/under production of duration due to the complete loss of the ability to hold a representation across a gap in time (6, 78). Similarly, anterograde amnesic patients with severe episodic memory disorders resulting from bilateral temporal lobe lesions, underestimate durations exceeding



15–20 s (82–84), and patients with right temporal lobe lesions are equally affected in the estimations of durations in the second to minutes range (85–87), which presumably involves memory mechanisms. Also reproduction tasks, which require estimating a target duration in order to reproduce it, lead to inaccurate and variable estimations particularly in patients with right temporal lobe lesions (85–87). While short-term and working memory are involved in both the estimation and the reproduction of brief intervals, long-term memory is implicated in timing durations in seconds to minutes range and the under estimation of long durations would reflect a defective retrieval of information in episodic memory, consecutive to medial temporal lesions. Conversely, production tasks which require producing a target duration when given in a conventional unit (seconds or minutes), would entail the comparison with a “typical” duration acquired through life's experiences and stored in semantic or procedural memory (88). Although this ability might be spared in some amnesic patients (84), it probably requires both right and left medial temporal lobe mechanisms, as patients with either left or right medial temporal lobe lesions overestimated time, suggesting that medial temporal lobe structures are bilaterally involved in the production of intervals in the 1 to 8 min range (89). However, as patients with right medial temporal lobe lesions showed no impairments in a verbal estimation task that also requires the use of chronometric units, patients' deficits in producing conventional intervals could be partly due to less attention to the passing of time (89).

Moreover, the temporal lobe, and particularly the hippocampus, could participate in the determination of temporal expectancy, which is a continuously updated function of memory, within a fronto-hippocampal circuit modulating the memory stage of the SET. This memory complex, working in tandem with a fronto-striatal circuit which is the basis of the clock stage, would update temporal expectancy on a trial-by-trial basis and provide, once the expected signal or event occurs, an integrated tally of how

the expectation evolved over time (90). Owing to dense connections between the hippocampus and the striatum (91), the former could also act as a regulator of the dynamic firing threshold in striatal spiny neurons (7), thus contributing to the encoding of durations. A further possibility is that the hippocampus might be involved, in tandem with the ventral/medial striatal neurons, in the decision-making processes downstream of the clock stage (64, 78), most likely via inhibitory control of action sequences (92).

#### **STUDIES IN TRAUMATIC BRAIN INJURED PATIENTS. DOES TIME PERCEPTION DEPEND ON UNIMPAIRED ATTENTION AND WORKING MEMORY?**

Temporal impairment in patients with TBI is expected considering the high incidence of frontal lobe and cognitive dysfunction associated with TBI. Timing dysfunctions have in fact, been documented in patients with focal frontal lesions (55, 56, 70) and attributed to deficits in attention and working memory processes resulting from frontal damage. In view of the fact that slowing of processing speed, reduced attentional capacities, and working memory deficits commonly follow TBI (93), few studies investigated the effect of such disorders on accuracy and precision of duration judgments in TBI (94–99). Some studies employed time reproduction tasks (94, 96, 97) eventually coupled with a time production task (97) and some a time verbal estimation task (94, 98, 99) in which participants are exposed to time intervals and subsequently asked to verbally estimate duration length. The latter is thought to be preferable for studying the sense of time-in-passing (100) since is a measure of how an individuals' subjective duration of time relates to actual units of time. However, the time durations tested in the abovementioned studies ranged between 4 and 60 s, thus limiting the investigation to supra-second interval timing. Moreover, investigations were mostly conducted on mixed samples of severe and moderate TBI (94, 98, 99), hence making it difficult to discern the impact of brain injury severity on temporal performance. Only two recent studies (95, 101) employed a time discrimination task to examine temporal abilities in TBI patients with short durations. Indeed, compared to time reproduction and production, this task appears to be the best method to detect temporal differences when short intervals are used (102). Additionally, the abovementioned studies were conducted on severe TBI patients in which the prevalence of diffuse axonal injury (103) is likely to result in working memory and attentional deficits, thus affecting temporal performance.

In general, temporal dysfunctions were observed in severe and moderate TBI patients when tested using long intervals, probably exceeding their working memory span (94, 98); likewise, lower accuracy was reported in discriminating a short interval (500 ms as compared to the 1300-ms interval) (101), whereas severe TBI patients and control subjects equally over-produced a brief duration (500 ms) (95). More specifically, variability in time reproduction seems to be correlated with working memory and processing speed performance [at least in patients affected by severe head injury, Ref. (96, 97)], while the variability index for the production task is correlated only with the processing speed measure (97). These findings suggest that severe TBI patients have difficulty in maintaining a stable representation of duration, probably due to impaired sustained attention and working memory.

Indeed, despite enduring episodic memory deficits, timing performance in TBI is no longer impaired after a year of recovery (99), implying that other cognitive factors are associated with supra-seconds interval timing. Similarly, TBI patients required working memory and speed of processing abilities to discriminate intervals shorter than a second (101). The observation that no differences were found in a time production task between severe TBI patients and control subjects (101) further suggests that temporal impairment in TBI may not be at the level of the internal clock, as temporal production minimizes the demands on additional cognitive processes, while performance correlates with spontaneous tempo as measured through a tapping task (104).

Lastly, deficits in predictive eye movements during the tracking of a temporally regular stimulus were observed in a group of mild TBI (21) and correlated to measures of working memory and executive control. Through tracking of a temporally predictable target, smooth pursuit eye movements are programmed to compensate for visual delays and minimize mismatches between eye and target position and velocity. Such predictive movements are based on an implicit representation of elapsed time (105) and errors in target prediction may be indicative of disorders in the temporal processing component of the task (106). The fact that working memory and executive deficits were correlated with oculomotor measures suggests that parameters of predictive eye movements may be used as a metric of these functions in both the normal population and TBI patients, and as a sensitive assay of damage to the underlying neural connections after TBI (21).

#### **RELATIONSHIP BETWEEN TIME ESTIMATION AND COGNITION**

The evidence discussed above emphasizes the complex relationship between both cognitive and contextual factors involved in time estimation. Indeed, this association may be specific either to the time estimation task, or to the range of the target durations employed as for example, episodic memory is differentially involved in reproduction tasks (as opposed to intervals production) and in the estimation of durations exceeding the working memory span. As a case in point, results show that changes in time estimation with aging are related to different cognitive deficits depending on the conditions in which temporal judgments are collected. Shorter reproductions in older adults are better explained by working memory limitations, whereas longer productions in older adults are better explained by slower processing speed (107). Since processing speed is assumed to be related to the clock speed, such observation would suggest that the slowing of information processing with normal aging reflects the slowing of the internal clock rate (108) and would explain age-related changes in duration judgment. Similarly, increased variability in intervals production in TBI patients correlates with processing speed measures, such that temporal performance in this task may not reflect deficits specifically related to timing, but rather to generalized attention and processing speed problems (107). Conversely, increased variability in the reproduction task is related in TBI patients, to updating dysfunctions (101) suggesting that these patients may have difficulties in forming a stable representation of duration due to disorders in working memory. Likewise, lower performance in executive control and working memory correlates with increased

variability in measures of implicit timing in mild TBI (21) suggesting that such cognitive factors may influence predictive behaviors based on temporal regularities in stimulus presentation.

Regarding long-term memory, several studies showed that accurate reproduction and discrimination of long durations rely on preserved episodic memory. However, data on duration production tasks are less consistent, as episodic memory should not be necessary in this kind of task, while patients with either left or right medial temporal lobe lesions under-produce intervals in the minutes range (89). Conversely, a semantic/procedural knowledge must be accessed to produce a target duration given in conventional time units and patients with unilateral right temporal lobe resection seem to be selectively impaired in time production abilities (107). Such observation would suggest that the semantic memory involved in the production task depends on the right medial temporal lobe (107); alternatively, patients' deficits in producing conventional intervals could be partly due to less attention to the passing of time (89). **Table 2** summarizes the findings on time distortions in brain damaged patients, outlining the potential mechanism of time dysperception in the considered populations.

CONCLUSION

In this paper we surveyed time distortions in clinical populations who have pathophysiological structural alterations in brain areas recently implicated in normal human timing. Given that one can dissect the role of different cognitive processes from the behavioral data gathered in timing paradigms, we could identify the nature of specific timing disorders in different brain damaged populations. We purposely highlighted the interaction between

cognitive impairments and loss of accuracy and/or precision in duration judgments, in order to characterize such relationship in each group.

We concluded that while timing variability in TBI patients is not consequent to dysfunctions at the clock stage, but rather related to attentional, working memory and executive functions disorders, medial temporal lobe damage affects the memory component, and possibly the downstream decision-making stage, of the temporal information processing model.

As for the complex relationship between both cognitive and contextual factors involved in time estimation, we posited that the correlation between timed and other cognitive behaviors derive in reproduction and discrimination tasks, from the coincidental co-variation in the cognitive components (e.g., working memory) shared by the two functions. Conversely, variability in production tasks is better explained by variations in processing speed measures (as indexed by reaction time performance), suggesting that time estimation could be a major contributor to reaction time. Indeed, processing speed has been proposed as a “cognitive primitive” participating in several aspects of cognitive functioning, such that variations in the efficiency or effectiveness of specific cognitive processes derive from changes in the speed with which many cognitive operations can be executed. If we assume that the rate of information processing reflects the internal clock rate, then changes in the clock speed due to a neurological disorder would impact the promptitude of executing many different types of processing operations, lastly affecting several cognitive activities.

Following this line of argument, interval timing is a solid construct to study the cognitive effect of a brain insult in specific areas

Table 2 | Summary of pathophysiological distortions in time in neurological and traumatic brain injured patients.

Timing paradigm	Findings	Intervening cognitive factors
Duration estimation (ms)	Patients with R medial temporal lobe resection more variable in discriminating short intervals (64) Severe TBI patients less accurate when discriminating a short interval (101). The performance significantly correlates with working memory and speed of processing indices	The R medial temporal lobe is involved in controlling the variability of time processing at the level of the decision stage TBI patients seem to refer to cognitively controlled timing to discriminate intervals shorter than a second
Duration estimation (s)	Patients with R prefrontal lesions show robust deficits when discriminating longer durations (56, 57)  Patients with bilateral temporal lobe lesions are affected in the estimation of durations in the second to minutes range (85–87) Underestimation of long intervals after functional inhibition (59) or lesion (58) to the R parietal lobe Severe and moderate TBI patients significantly different when tested in durations exceeding their working memory span (94, 98)	The prefrontal cortex sub serves non-temporal processes as sustained attention and working memory required to time long durations Amnesic patients underestimate longer durations due to defective retrieval of temporal information in episodic memory A right fronto-parietal network is involved in sustaining attention to time TBI patients have difficulty in maintaining a stable representation of duration due to impaired sustained attention and working memory
Interval production	Patients with R and L medial temporal lobe lesions over produce intervals in the minutes range (89) Time pacing at the 1-s tempo is accelerated in some severe TBI patients and slowed down in others (97) No differences in severe TBI patients when reproducing intervals (101)	Poorer allocation of attention to the passage of time in patients with medial temporal lesions In creased variability in temporal performance due to processing speed problems Temporal impairment in TBI patients may not be at the level of the internal clock

The potential mechanism of time dysperception in the different samples is also highlighted.

and it has been already posited as a model system to study cognitive aging. Moreover, owing to the extensive overlapping between neural circuits involved in high-level cognitive functions and interval timing, temporal tasks could be used not only as a metric of intellectual functioning, but also as a sensitive assay of damage to the underlying neural substrate.

As time is a fundamental “basic unit of ability” (3) on which other cognitive and behavioral processes are based, future studies should definitively answer the question of whether time distortions are a manifestation of, or a mechanism for, cognitive and behavioral symptoms of brain damage.

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